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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/586,744	06/02/2000	John Joseph Harrington	9584-0017-999	7865

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	PAPER NUMBER
1652	33

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Please find below and/or attached an Office communication concerning this application or proceeding.

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Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☒ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 3/11/03 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☒ will be entered ☐ will not be entered and the status of the claims will be as follows:

   Claims allowed: 1-6
   Claims objected to: _____
   Claims rejected: 7-73

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4. ☐ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because _____

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other see Office Action

Advisory Action

1. Applicants' amendment-after-final filed 3.11.03 (Paper No. 31) is acknowledged.

2. Applicants letter filed 3.11.03 (Paper No. 32) and Offer to Surrender Patent is also acknowledged.

The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

3. Claims 1-73 are under consideration in this examination.

4. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

5. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

6. ***New Matter***

Claims 7-73 are rejected under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought.

Applicant argue that 'It is well settled that amendments that replace subject matter incorporated into an application by reference with the **actual text and figures** of the incorporated document do not constitute new matter See, e.g., M.P.E.P 2163.07 (b).

By Applicants own arguments, it is acknowledged that replacing subject matter incorporated into an application by reference with the **actual** text and figures of the incorporated document do not constitute new matter. Therefore incorporation of the actual text or figures from Harrington and

Lieber, 1995, J. Biol. Chem. 270 : 4503 would be proper. However, neither the issued patent (U.S.P. 5,874,283) nor the incorporated reference of Harrington and Lieber (1995), describe the method steps of claims 7-73. Applicants may point to the actual text of the referred article of Harrington and Lieber (1995) or the issued patent in overcoming this rejection. There is no support in the instant specification or the incorporated reference that identifies the actual text which would indicate that the invention of claims 7-73 was conceived at the time of filing this application. Further there is no basis for methods of cleaving, detecting or formation of a hybridization complex or a kit - where the target nucleic acid having a first or second portion, or where **3'-probe** comprises a 3'-flap region that is 1, 1-10 or 1-20 nucleotides in length (Claims 14-16, 31-33, 48-50, 56-58, 62-64). How is a single nucleotide cleaved ? It may also be noted that the incorporated reference shows cleaving of the DNA molecule (not RNA) therefore has no basis for 'polynucleotide' cleavage - RNA is not cleaved by FEN-1 (Harrington and Lieber, 1995, see page 1240, column 2, last 2 lines). Similarly there is no basis for 'polynucleotides' or 3' polynucleotides in the claims, whether it is for methods of cleavage or complexes or kits.

Effective incorporation by reference is lacking. Applicants must clearly point out where in specification (or issued patent)or in the properly incorporated reference such methods or complexes have a clear-cut basis, or the invention was conceived at the time of filing this application.

Applicants cite numerous case laws, including *In re Voss*, 194 USPQ 267 (CCPA 1977) *and re Hughe,* 193 USPQ 141 (CCPA 1977). However, since the incorporation of the subject matter is improper, the referenced case laws do not apply.

Applicants' Arguments :

Applicants misinterpret Examiner's Office Action by stating that 'The Examiner acknowledges these amendments as proper (see Office Action, page 3, lines 9-10), yet at the same time contends Claims 7-73 are based upon new matter'.

In response the Office Action, page 3, lines 9-10 is reproduced here and underlined as follows:

'Therefore incorporation of the actual text or figures from Harrington and Lieber, 1995, J. Biol. Chem. 270 : 4503 would be proper. However, neither the issued patent (U.S.P. 5,874,283) nor the incorporated reference of Harrington and Lieber (1995), describe the method steps of claims 7-73'.

As indicated above the language does not in any way acknowledge that incorporation of the amendment by the applicants was proper - it merely clarifies what the legal standards are and that the incorporation of actual text or figures is acceptable. Applicants clearly missed or ignored the sentence following the underlined statement - which clearly conveys that 'neither the issued patent (U.S.P. 5,874,283) nor the incorporated reference of Harrington and Lieber (1995), describe the method steps of claims 7-73'.

The issue in all these claims is incorporation of **'3' polynucleotide probe'** in the method step. Applicants point to Column 11, lines 3-48 and Column 42, lines 63 through Column 43, lines 36 of the issued patent for support or for proper incorporation of actual text.

However, this is not the case, and it can be seen that while cited paragraphs describe the method steps using 5' polynucleotide probe there is no mention of **'3' polynucleotide probe'** in the

method steps and therefore the incorporation is improper. Further, no where is the range '1-10 or 1-20 nucleotides in length' described or taught.

Further, Applicants' attention is drawn to column 46, lines 65-67 of the issued patent which states that 'no detectable cleavage of 3' flap structure was observed even in the presence of 15 U of FEN-1- which indicates that 3' end is not cleaved' and therefore unsuitable for the method.

7. ***Written Description***

Claims 7-10, 14-27, 31-44, 48-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a method of cleaving a polynucleotide (claims 7-10, 14-27), a method of detecting the presence of target nucleic acid (claims 31-44), a hybridization complex (claims 48-58) and a kit for detecting the presence of a target nucleic acid (claims 59-70). The instant claims contain no limitations that define the structures of the claimed endonuclease (or FEN-1 SEQ ID NO :) or the strand that FEN-1 uses as substrate, used for cleaving a polynucleotide comprising the 3' and 5' regions or that used in the detection method or for hybridization complex and kit. FEN-1 cleavage is flap strand specific and independent of flap strand length [Harrington & Lieber, 1994, see abstract].

Applicants' argue that claims 7-73 are rejected for lack of written description. That is not the case. Only claims 7-10, 14-27, 31-44, 48-70 are rejected.

Applicants further argue that the original disclosure teaches diagnostic methods and probe polynucleotides capable of specific hybridization to the target and forming, as a result of such hybridization, a 5'-flap structure which can be cleaved by FEN-1.

In response, it is pointed out the claims (e.g. claims 7-9, 14-20) do not recite endonuclease FEN-1 and its structure (e.g. claims 7-10, 14-27, 31-44, 48-70) as argued. While the specification describes three species of FEN-1 polypeptides - human FEN-1 (SEQ ID NO : 1), murine FEN-1 (SEQ ID NO : 3) and yeast FEN-1 (SEQ ID NO : 5) bearing close sequence homology or the isolation of endonuclease activity RAD2 : SEQ ID NO : 7, calf thymus, rabbit reticulocytes, etc., but which differ is other respects and is not representative of the entire 'FEN-1' genus.

New Arguments :

Applicants argue that the instant application describe a representative number of species of endonucleases adequate to provide written description support for the genus. For example, the disclosure describes three species of FEN-1 polypeptides : human FEN-1 (SEQ ID NO : 1), murine FEN-1 (SEQ ID NO : 3) and yeast FEN-1 (SEQ ID NO : 5). Further species of FEN-1 isolated from nuclear extract of calf thymus, rabbit reticulocytes, Chinese hamster fibroblast, etc., are described. These species adequately represent the genus of suitable endonucleases.

Applicants further argue that amended claims 7-10 & 14-20 describe the cleavage step functionally. Citing case laws in general - *In re Herschler*, 200 USPQ 711 (CCPA 1979); *In re Halleck*, 164 USPQ 647 (CCPA 1970); *In re Fuetterer*, 138 USPQ 217 (CCPA 1963); *In re Boller*, 141 USPQ 740 (CCPA 1964); and *In re Fuetterer* in particular, Applicants argue that a functional

description of a genus of salts was held proper in a claim to a composition comprising the salts and other ingredients. In *In re Herschler*, a functional description of a genus of steroids was held proper in a claimed method of enhancing the penetration of a physiologically active steroidal agent across an external barrier membrane of a human or animal subject using an effective amount of DMSO.

In response, and as per the decision affirming in case of *In re Fuetterer*, 138 USPQ 217 (CCPA 1963), the board stated: * * * There is no indication that the function asserted for the salts is known in the art so that the suitable salts could be readily determined without undue experimentation nor is there any criteria given in the disclosure by which it could be fairly readily determined what salts are suitable. It seems that the determination of suitable salts thus would require testing by trial and error many thousands of known salts to ascertain those which would function in the manner required by the claims, and such a burden should not be required of the public or even by those skilled in the art. Accordingly, we will sustain this rejection.

Likewise in the instant case, claims drawn to a method of cleaving a 5'-polynucleotide by FEN-1 does not functionally or structurally define the double flap structure used as substrates in the method [nor are structures well known in the art prior to the instant filing], for being acted upon by the FEN-1 polypeptide, and that the determination of suitable substrates or double flap structures would require testing by trial and error many known or unknown double flap structures to ascertain those which would function in the manner required by the claims, and would involve undue burden upon those skilled in the art.

8. Claims 7-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With regard to claims 7-73, directed to a nucleic acid probe that specifically hybridizes to another or target nucleic acid(s), Applicants have not sufficiently defined the conditions under which the hybridizations are to take place. Nucleic acid hybridization assays are extremely sensitive to the conditions in which they are performed. The buffer composition, pH, temperature, length of time, salt concentrations, quality and source of template nucleic acid, are all variables which determine the reproducibility of a given hybridization experiment. Given the unpredictability of the art and the nature of hybridization experiments in general, it is not sufficient to merely cite hybridization without a clear and explicit recitation of the conditions associated with the hybridization. For example, the definition of stringency as it pertains to hybridization conditions is subject to interpretation and is different from laboratory to laboratory. The specification provide no definition of high, medium or low stringency hybridization conditions used. Therefore, without a clear and explicit recitation of the conditions which were actually used by Applicants in isolating the claimed polynucleotides which hybridize to the disclosed sequences, the skilled artisan would not be able to practice the claimed invention and would not be reasonably apprised of the metes and bounds of the claimed invention. Without such guidance, the experimentation left to those skilled in the art is undue.

Applicants arguments elude description to hybridization conditions. No specific hybridization conditions are described in the col. 39, line 65 through col. 40, line 18; or columns 49-51, of the issued patent as argued.

New arguments :

Applicants argue that the incorporated H & L article teaches 'hybridization conditions under which 5' cleavage was detected, without pointing to the pages/lines where such conditions are described; whether such hybridization conditions be low, medium or high stringency.

It appears these cleavage conditions may not be specific to the method claimed, in which case such conditions can be made part of the specification, and in being non-specific to the methods claimed the hybridization conditions may be added into the claims.

9. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: cleaving the 5' flap labeled structure by FEN-1, releasing the nucleotide in the flap strand; incubating with FEN-1 and detection the release of nucleotides (polynucleotide) of the flap strand and quantifying the released label as a measure of abundance of the target polynucleotide in the sample. The clarity of the steps is important.

Applicants argue that the amended claim 7 recite 'selectively cleaving' - which step subsumes (or encompass) the cleavage, release and incubation steps the Patent Office believes are omitted. While the disclosure at Col. 11, line 11 recites 'incubating with FEN-1' which when read in the

context of the complete disclosure, skilled artisans would immediately recognize that this passage supports step (b) as presently drafted.

In response it is stated that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, an important method step cannot be assumed and such a step is not encompassed by the claim.

New argument :

Applicants argue that the amended claim 7 is complete, and the claimed subject matter need not be described *in haec verba* to satisfy the written description requirement.

This is not a written description rejection. This rejection is made under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements.

As stated earlier, an important method step cannot be assumed and such a step is not encompassed by the claim.

The omitted elements are: cleaving the 5' flap labeled structure by FEN-1, releasing the nucleotide in the flap strand; incubating with FEN-1 and detection the release of nucleotides (polynucleotide) of the flap strand and quantifying the released label as a measure of abundance of the target polynucleotide in the sample. The clarity of the steps is important.

Applicants inclusion of 'a 5'-polynucleotide probe capable of being cleaved by a FEN-1' in claim 7, line 5, is noted. However, the limitation 'a 5'-polynucleotide probe capable of being cleaved

by a FEN-1' does not reflect that the method step exclusively involves 'incubating or cleaving by a FEN-1.

Amending the claim to include the phrase 'a 5'-polynucleotide probe which is cleaved by a FEN-1 polypeptide' instead of 'a 5'-polynucleotide probe capable of being cleaved by a FEN-1'.

Further addition in step (c) detecting release of label and.....cleavage [is suggested], to clearly define the method steps.

10. Claims 1-6 are allowed as indicated before.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T. Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
March 31, 2003